Economic evaluation of trans-perineal devices for local anaesthetic prostate biopsies.

Supplementary Material

Edward CF Wilson,[1*] Alice Wreford,[1] Priya Tamer,[2] Kelly Leonard,[2] Hannah Brechka,[2] Vincent J Gnanapragasam[2,3,4]

1 Health Economics Group, Norwich Medical School, University of East Anglia, Norwich, UK

2 Cambridge Urology Translational Research and Clinical Trials Office, Cambridge Biomedical Campus, Cambridge, UK

3 Department of Urology, Cambridge University Hospitals Trust, UK

4 Division of Urology, Department of Surgery, University of Cambridge, UK

Corresponding author: Dr Ed Wilson. edwilson@phmr.com

Funding
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study/project is funded by a NIHR i4i Product Development Award (II-LB-0716-20001). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Ethical approval
Ethical approval was not required for the decision model component of the NIHR award reported here. However, the clinical study was reviewed and received favourable ethical opinion by the East of England – Cambridge Central Ethics Committee (REC 18/EE/0272, IRAS Project ID: 242948).

Conflicts of interest/Competing interests
VJG is the inventor and patent holder of the CamPROBE device. All other authors confirm they have no conflicts of interest to declare.

Consent to participate
Not applicable

Consent for publication
Not applicable

Availability of data and material (data transparency)
Not applicable

Code availability (software application or custom code)
Model code is available on request from the corresponding author.

Authors' contributions
EW developed and analysed the model and led drafting, editing and review of the manuscript. AW conducted the microcosting and revised and edited the manuscript. PT revised and edited the manuscript. KL revised and edited the manuscript. HB revised and edited the manuscript. VJG contributed to development of the model and drafting ,editing and review of the manuscript.

Appendices

Appendix 1: Fitting distributions to probabilities

Sensitivity and specificity of mpMRI and biopsy

As there are four possible disease states (no cancer; NC, clinically non-significant cancer; CNS, intermediate risk; IR and high risk; HR), and three possible diagnoses (NC, CNS and CS where CS includes both IR and HR), the sensitivity and specificity are captured in a 4x3 contingency table, rather than a 2x2 table when there are only two disease states and two diagnoses.

Faria et al.[9] present mean and 95%CIs for each element (Supplementary tables 6 and 7 for TRUSB and mpMRI respectively). As there are three possible outcomes from a test, a multinomial distribution was required to model these. Using a previously developed search algorithm,[12] Dirichlet, Connor-Mosimann and modified Connor-Mosimann distributions were fitted to the data. This uses an algorithm to find a set of parameters for each distribution that has the lowest sum of the squared deviations between the means and 95%CI bounds. The distribution and set of parameters associated with the lowest sum of squared deviations was selected as the best fitting model.

Long term transition probabilities

Ideally long-term transition probabilities should also be fitted using multinomial distributions. However, as the individual probabilities were 'low', independent beta distributions provided a clearer and more expedient approach. The parameters of the betas were calculated from the reported mean and 95% confidence intervals from Table 9, Faria et al.[9] supplement.

Appendix 2: Microcosting

As part of the prospective case series, a microcosting exercise was undertaken on a sample of CamPROBE and transrectal biopsies (n=17 each). All biopsies were conducted at Cambridge University Hospitals NHS Trust (Addenbrooke's Hospital).

Data recorded were time to perform biopsy procedure, volume of local anaesthesia used and other consumables and equipment, extracted on to a data collection form (Appendix 3).

A large number of consumables are common to both procedures, and so are excluded from the incremental analysis. However, we present them here for completeness.

Results

Table A2.1 shows a point estimate difference of 4.1 minutes procedure time between CamPROBE and TRUSBx, and a 0.9mL increase in anaesthetic use. Given the small sample size, we do not perform any statistical analysis on these differences, and for the purposes of the decision model, we assume both procedures take the same time and use the same volume of anaesthetic (lidocaine).

Table A2.1: Comparison of procedure time and volume of anaesthetic, mean (SD) from lead centre in the CamPROBE study (ref 7)

	CamPROBE (n=17)	**TRUSB (n=17)**	**Difference**
Procedure time (minutes)	24.4 (8.88)	28.5 (6.8)	-4.1mins
Anaesthesia (mLs)	10.9 (3.1)	10 (0)	+0.9ml

Reusable equipment common to both arms are:

- Linear transducer endocavity US probe (CamPROBE)
- Prostate triplane E14C4t US probe (TRUS)
- Ultrasound machine
- Suitable couch and legs

These are not costed as our focus is on the consumables. Common consumables cost £43.49, with TRUSBx-specific consumables costing an extra £19.81, and for CamPROBE £3.10 (Table A2.2). Note importantly, this excludes the cost of the CamPROBE device itself as per the base case analysis (see body text section Methods, Analysis). The difference in cost is therefore -£16.71 per procedure. This can be interpreted as the maximum per-procedure price of CamPROBE for the consumables cost to be equal between the two techniques. As two CamPROBEs are required per procedure, the maximum unit cost would therefore be half of this (£8.36).

Table A2.2: Consumables quantities and cost, mean (SD). 2018-19 prices

Item	Unit Cost	Unit	Quantity	Cost
Consumables common to both arms				
18 gauge biopsy needle	£135.00 [b]	Box, 5	1	£27.00
Condoms	£27.77 [b]	Box, 500	1	£0.06
Ultrasound lubricant gel	£3.54 [b]	5L	10mL	£0.01
Sterile Gloves	£78.60 [b]	Case, 50 pairs	2 pairs	£3.14
Dressing Towel	£0.20 [c]	1	1	£0.20
Biopsy Cassettes	£0.10 [c]	1	12	£1.20
10mL Syringe	£3.72	Pack, 100	2	£0.07
1 % lignocaine / lidocaine	£11.00 [d]	20mL	20mLs	£11.00
Glycerol Suppositories	£0.09 [d]	1	1	£0.09
Ciprofloxacin	£0.092 [d]	1	7x500mg	£0.64
antiseptic wash	£2.59 [b,e]	600mL	10mL	£0.04
Sterile saline	£3.72 [b,f]	10x100mL sachets	10mL	£0.04
Total				*£43.49*

			TRUSBx (n=17)	CamPROBE (n=17)	TRUSBx (n=17)	CamPROBE (n=17)
Technique specific consumables						
Clip on needle guide for US transducer	£300.00 [b]	Box, 18	1		£17.00	
Spinal Needle (Quincke) 22G x 7.00in	£28.08 [b]	Pack, 10	1		£2.81	
Cotton Gauze	£0.90	Pack, 100		~10		£0.10
steristrips	£7.74	Pack, 50		2		£0.31
Orange Needles	£2.89 [b]	Pack, 100		2		£0.06
Green Needles	£1.78 [b]	Pack, 100		2		£0.04
Sterile Drape with Adhesive	£111.46 [b]	Pack, 50		1		£2.23
Shallow sterile plastic tray	£18.20	Case, 50		1		£0.36
Total (technique specific, excluding CamPROBE)					*£19.81*	*£3.10[e]*
Total (all consumables, Excl CamPROBE device)					*£63.30*	*£46.59[e]*

b. Source of unit costs: local prices; c. Source of unit costs: estimate; d. Source of unit costs: Drug Tariff, March 2019;[19] e. 600ml bottle = £2.59. f. £3.72 per 10x100ml sachets. g. Base case analysis excludes cost of CamPROBE: see Methods, Analysis in main body for details.

Appendix 3: Microcosting Data Collection Form

V1.0 24/01/19

Cambridge Urology
Translational Research & Clinical Trials

CamProbe MicroCosting

Today's date	Date of procedure	Initials of research nurse
_____/_____/_____	_____/_____/_____	_____

Please complete the information below as fully as possible. If there are any additional items used please add overleaf. For any further queries please email ed.wilson@uea.ac.uk. Thank you!

Patient preparation prior to procedure	
Item	
Prophylactic antibiotic: □ Ciprofloxacin □ Other (please specify): _____ □ None	Dose:
Glycerine: □ Yes □ No	Dose:
Other (please specify):	

During the procedure	
Approx time patient entered room: _____:_____	
STAFF PRESENT:	
Type	Grade

CONSUMABLES (*approx*. number or total mls as appropriate)

Disposable biopsy device gun/needle		Anaesthetic (mls)	
Biopsy guide		Antiseptic wash (mls)	
Other Needles		Saline (mls)	
CamProbe devices			

Other (please tick and/or write in any other items):

□ Swabs	□ Ultrasound gel
□ Urine pot and dipstick	□ Gloves
□ Syringes	□ Dressing pack
□ Sheath	□ Formalin pot
□ Lubricant	

Approx time patient exited procedure room: _____:_____

After the procedure	
Post biopsy antibiotic prescribed: □ Ciprofloxacin □ other (please specify): _____	Dose:

UEA University of East Anglia

Academic Urology Group
University of Cambridge

NHS
National Institute for Health Research

Appendix 4: Definition of population who potentially benefit from further research

In 2018/19, the NHS Schedule of reference costs reports that 39,211 transrectal ultrasound guided biopsies of the prostate were performed in the NHS in England (NHS Reference Costs 2018/19,[17] sheet 'Total HRGs', currency code LB76Z [cell C1728]). Given a 10-year time horizon (representing the time for which the information is assumed to be useful), and discounting at 3.5% yields a beneficial population of 337,516.

Appendix 5: Stability testing

The model was run 30 times with increasing numbers of iterations, and the coefficient of variation of the estimate of mean incremental net benefit and of standard error of incremental net benefit calculated. The coefficient of variation of the estimate of mean incremental net benefit is approximately 1.97% at 200,000 iterations, with that of the standard error at 0.28% (Table A5.1). 200,000 iterations were therefore considered to yield sufficiently stable results.

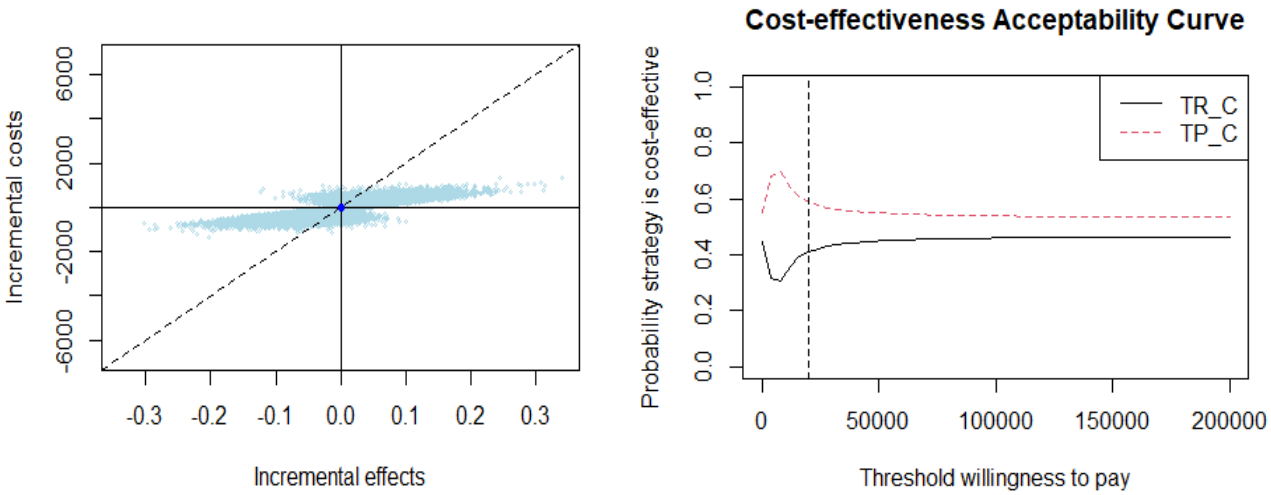
Table A5.1: Coefficient of variation of estimate of mean and standard error of incremental net benefit as a function of number of Monte Carlo simulations

iterations	Mean	SE
10	2.3996	0.2677
1,000	0.2248	0.0355
5,000	0.1192	0.0150
10,000	0.0773	0.0121
20,000	0.0471	0.0091
50,000	0.0330	0.0044
100,000	0.0264	0.0042
200,000	0.0197	0.0028
250,000	0.0164	0.0021
500,000	0.0119	0.0013

Incremental Net Benefit calculated at £20,000 per QALY

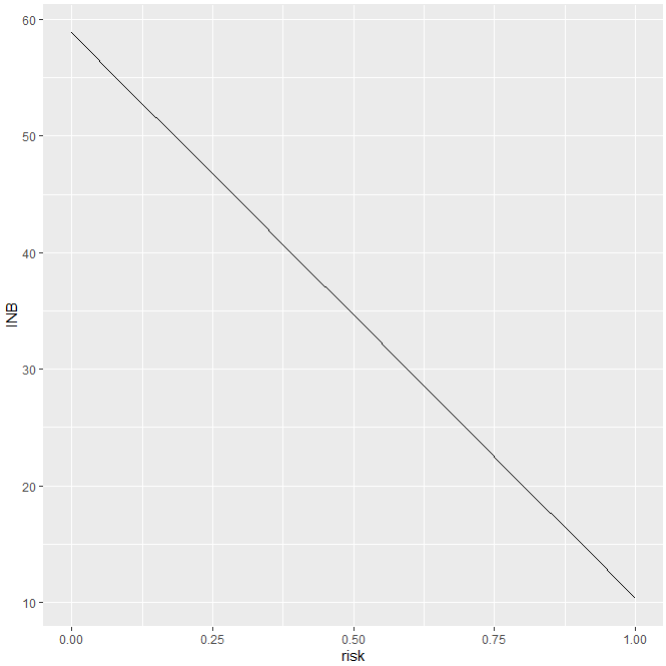
Appendix 6: Additional data and figures

Figure A6.1: (a) Scatterplot of cost-QALY pairs and (b) Cost-effectiveness acceptability curve (base case)



TR_C = transrectal biopsy; TP_C = transperineal biopsy

Figure A6.2: One-way sensitivity analysis of INB vs risk of infection



Infection risk (x-axis) expressed as a proportion of that of TRUSB. Calculated at a zero price of TPUSBx device.
INB = Incremental Net Benefit (£)

Data for Figure 3a are presented in Table A6.1.

Table A6.1: One-way sensitivity analysis on price of TPUSBx device

	TRUSBx		TPUSBx		Increments		
Price*	Cost	QALYs	Cost	QALYs	Cost	QALYs	Net Benefit**
0	5051.523	10.291	5021.911	10.292	-29.612	0.001	58.87979
10	5051.523	10.291	5029.165	10.292	-22.358	0.001	51.62605
20	5051.523	10.291	5036.418	10.292	-15.105	0.001	44.3723
30	5051.523	10.291	5043.672	10.292	-7.851	0.001	37.11856
40	5051.523	10.291	5050.926	10.292	-0.597	0.001	29.86481
40.1	5051.523	10.291	5050.998	10.292	-0.525	0.001	29.79228
40.2	5051.523	10.291	5051.071	10.292	-0.452	0.001	29.71974
40.3	5051.523	10.291	5051.144	10.292	-0.379	0.001	29.6472
40.4	5051.523	10.291	5051.216	10.292	-0.307	0.001	29.57467
40.5	5051.523	10.291	5051.289	10.292	-0.234	0.001	29.50213
40.6	5051.523	10.291	5051.361	10.292	-0.162	0.001	29.42959
40.7	5051.523	10.291	5051.434	10.292	-0.089	0.001	29.35705
40.8	5051.523	10.291	5051.506	10.292	-0.017	0.001	29.28452
40.81	5051.523	10.291	5051.514	10.292	-0.009	0.001	29.27726
40.82	5051.523	10.291	5051.521	10.292	-0.002	0.001	29.27001
40.83	5051.523	10.291	5051.528	10.292	0.005	0.001	29.26275
40.84	5051.523	10.291	5051.535	10.292	0.012	0.001	29.2555
40.85	5051.523	10.291	5051.543	10.292	0.02	0.001	29.24825
40.86	5051.523	10.291	5051.55	10.292	0.027	0.001	29.24099
40.87	5051.523	10.291	5051.557	10.292	0.034	0.001	29.23374
40.88	5051.523	10.291	5051.564	10.292	0.041	0.001	29.22649
40.89	5051.523	10.291	5051.572	10.292	0.049	0.001	29.21923
40.9	5051.523	10.291	5051.579	10.292	0.056	0.001	29.21198
41	5051.523	10.291	5051.651	10.292	0.128	0.001	29.13944
42	5051.523	10.291	5052.377	10.292	0.854	0.001	28.41407
43	5051.523	10.291	5053.102	10.292	1.579	0.001	27.68869
44	5051.523	10.291	5053.827	10.292	2.304	0.001	26.96332
45	5051.523	10.291	5054.553	10.292	3.03	0.001	26.23794
46	5051.523	10.291	5055.278	10.292	3.755	0.001	25.51257
47	5051.523	10.291	5056.004	10.292	4.481	0.001	24.78719
48	5051.523	10.291	5056.729	10.292	5.206	0.001	24.06182
49	5051.523	10.291	5057.454	10.292	5.931	0.001	23.33645
50	5051.523	10.291	5058.18	10.292	6.657	0.001	22.61107
60	5051.523	10.291	5065.433	10.292	13.91	0.001	15.35733
70	5051.523	10.291	5072.687	10.292	21.164	0.001	8.103584
80	5051.523	10.291	5079.941	10.292	28.418	0.001	0.84984
81	5051.523	10.291	5080.666	10.292	29.143	0.001	0.124466
81.1	5051.523	10.291	5080.739	10.292	29.216	0.001	0.051928
81.11	5051.523	10.291	5080.746	10.292	29.223	0.001	0.044674
81.12	5051.523	10.291	5080.753	10.292	29.23	0.001	0.037421
81.13	5051.523	10.291	5080.761	10.292	29.238	0.001	0.030167
81.14	5051.523	10.291	5080.768	10.292	29.245	0.001	0.022913

81.15	5051.523	10.291	5080.775	10.292	29.252	0.001	0.015659
81.16	5051.523	10.291	5080.782	10.292	29.259	0.001	0.008406
81.17	5051.523	10.291	5080.79	10.292	29.267	0.001	0.001152
81.18	5051.523	10.291	5080.797	10.292	29.274	0.001	-0.0061
81.19	5051.523	10.291	5080.804	10.292	29.281	0.001	-0.01336
81.2	5051.523	10.291	5080.811	10.292	29.288	0.001	-0.02061
82	5051.523	10.291	5081.392	10.292	29.869	0.001	-0.60091
83	5051.523	10.291	5082.117	10.292	30.594	0.001	-1.32628
84	5051.523	10.291	5082.842	10.292	31.319	0.001	-2.05166
85	5051.523	10.291	5083.568	10.292	32.045	0.001	-2.77703
86	5051.523	10.291	5084.293	10.292	32.77	0.001	-3.50241
87	5051.523	10.291	5085.019	10.292	33.496	0.001	-4.22778
88	5051.523	10.291	5085.744	10.292	34.221	0.001	-4.95316
89	5051.523	10.291	5086.469	10.292	34.946	0.001	-5.67853
90	5051.523	10.291	5087.195	10.292	35.672	0.001	-6.4039
100	5051.523	10.291	5094.448	10.292	42.925	0.001	-13.6576
110	5051.523	10.291	5101.702	10.292	50.179	0.001	-20.9114
120	5051.523	10.291	5108.956	10.292	57.433	0.001	-28.1651
130	5051.523	10.291	5116.21	10.292	64.687	0.001	-35.4189
140	5051.523	10.291	5123.463	10.292	71.94	0.001	-42.6726
150	5051.523	10.291	5130.717	10.292	79.194	0.001	-49.9264

* Per procedure price of TPUSBx device. **Net benefit calculated at £20,000 per QALY.

Table A6.2 shows the EVPI and EVPPI for groups of parameters at both a zero and maximum cost-effective price of CamPROBE, where the groups represent individual model parameters that would logically be collected together in a future clinical trial. The individual constituent model parameters are shown in Tables A6.3 (zero price of CamPROBE) and A6.4 (max price).

Table A6.2: Expected Value of Perfect Information

Parameter(s)	Per Person EVPPI*	SE**	% of total EVPI*	EVPPI for England over 10 years*
At zero price of CamPROBE				
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is IR cancer	£136.96	£3.43	82%	£46,225,000
EVPI	£167.00	--	100%	£56,366,000
At maximum price of CamPROBE (£81.17)				
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is IR cancer	£162.15	£3.42	83.66%	£54,730,000

probability of infection with TRUSB	£14.99	£0.69	7.73%	£5,060,000
long term prognosis	£13.06	£3.02	6.74%	£4,410,000
diagnostic accuracy of 1st TR & TP biopsy when true state is IR cancer	£8.93	£2.93	4.61%	£3,010,000
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is NC, and true state is HR cancer	£9.44	£3.29	4.87%	£3,190,000
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is HR cancer	£7.31	£3.15	3.77%	£2,470,000
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is NC, and true state is IR cancer	£8.25	£3.16	4.25%	£2,780,000
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is CNS cancer	£8.67	£3.01	4.47%	£2,930,000
diagnostic accuracy of 1st TR & TP biopsy when true state is CNS cancer	£5.49	£2.77	2.83%	£1,850,000
Prevalence of varying severity of CaP	£1.84	£0.52	0.95%	£620,000
diagnostic accuracy of mpMRI when true state is CNS	£1.84	£0.52	0.95%	£620,000
risk of death from sepsis	£1.64	£0.57	1.00%	£552,000
EVPI	£193.80		100%	£65,416,000

**note EVPI ≠ ∑EVPPI (and thus also ∑% of total EVPI ≠ 100%) due to interactions and correlations between input parameters. **Standard error of per person EVPPI arises due to the SAVI approximation method.[39] Figures shown for groups of parameters with EVPPI>£500,000*

Table A6.3: Full EVPPI by model parameter and groups of parameters (at zero price of TPUSBx device)

	Per Person EVPPI*	SE**	% of total EVPI*	EVPPI for England over 10 years*
p_TPUSB2_CNS_IR3	96.5	0.62	0.58	32,570,000

p_TRUSB2_CNS_IR3		91.78	0.69	0.55	30,980,000
p_TPUSB2_CNS_IR2		70.54	0.6	0.42	23,810,000
p_TRUSB2_CNS_IR2		63.88	0.69	0.38	21,560,000
p_TPUSB2_CNS_IR1		46.12	0.64	0.28	15,570,000
p_TRUSB2_CNS_IR1		37.03	0.78	0.22	12,500,000
	Group	136.9562	3.43005	0.82	46,224,920
	EVPI	167.00	--	100%	56,366,000

EVPPI of individual parameters with EVPPI over £100,000. Explanation of parameter names: the group of six parameters, p_TPUSB2_CNS_IR3 to p_TRUSB2_CNS_IR1 relate to the sensitivity and specificity of the second TP or TR biopsy in patients with intermediate risk (IR) cancer, following a first biopsy result of 'clinically non-significant' (CNS). Suffix 1 = outcome of NC, 2 = CNS, 3 = CS. Thus p_TPUSB2_CNS_IR3 = probability of the second TP biopsy giving a result of clinically significant cancer following a first (TP) biopsy result of CNS, when the true state of the patient is intermediate risk cancer. The EVPPI of the group together represents the value of eliminating uncertainty in second biopsy results following a first biopsy result of CNS, when the true state is intermediate risk cancer, and is the figure reported in Table A6.2.

Table A6.4: Full EVPPI by model parameter and groups of parameters (at max price of TPUSBx device (£81.17))

	Per Person EVPPI (£)	Standard Error	%total EVPI	EVPPI for England (£)
p_TPUSB2_CNS_IR1	67.21	0.67	0.350	22,690,000
p_TPUSB2_CNS_IR2	94.05	0.60	0.490	31,740,000
p_TPUSB2_CNS_IR3	121.39	0.55	0.630	40,970,000
p_TRUSB2_CNS_IR1	67.69	0.67	0.350	22,850,000
p_TRUSB2_CNS_IR2	93.78	0.59	0.480	31,650,000
p_TRUSB2_CNS_IR3	121.41	0.57	0.630	40,980,000
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is IR cancer	**162.15**	**3.42**	**0.837**	**54,730,000**
p_TRUSB_CC1	5.72	0.68	0.030	1,931,000
p_TRUSB_CC2	0.01	0.24	0.000	4,164
p_TRUSB_CC3	1.74	0.58	0.010	586,400
p_TRUSB_CC4	14.70	0.65	0.080	4,961,000
probability of infection with TRUSB	**14.99**	**0.69**	**0.077**	**5,060,000**
p_PF_dead_IRww	0.12	0.26	0.000	41,330
p_PF_dead_IRrp	0.17	0.27	0.000	56,010
p_mets_dead_IRww	1.16	0.48	0.010	390,300
p_PF_mets_IRww	0.92	0.43	0.000	309,900
p_PF_dead_CNS	0.16	0.28	0.000	53,320
p_PF_mets_CNS	0.65	0.40	0.000	219,900
p_PF_mets_HRrp	0.48	0.33	0.000	161,700
p_mets_dead_HRrp	0.13	0.26	0.000	42,760
p_PF_mets_IRrp	0.28	0.28	0.000	95,910

long term prognosis		**13.06**	**3.02**	**0.067**	**4,410,000**
p_TRUSB1_IR1	0.56		0.37	0.000	188,800
p_TRUSB1_IR2	0.48		0.35	0.000	162,700
p_TRUSB1_IR3	0.10		0.28	0.000	33,520
p_TPUSB1_IR1	0.39		0.33	0.000	130,100
p_TPUSB1_IR2	0.38		0.32	0.000	127,400
p_TPUSB1_IR3	0.04		0.24	0.000	12,490
diagnostic accuracy of 1st TR & TP biopsy when true state is IR cancer		**8.93**	**2.93**	**0.046**	**3,010,000**
p_TRUSB2_NC_HR1	0.25		0.27	0.000	83,700
p_TRUSB2_NC_HR2	0.90		0.45	0.000	303,300
p_TRUSB2_NC_HR3	0.68		0.40	0.000	229,700
p_TPUSB2_NC_HR1	0.02		0.23	0.000	6,839
p_TPUSB2_NC_HR2	0.19		0.27	0.000	63,810
p_TPUSB2_NC_HR3	0.13		0.25	0.000	43,650
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is NC, and true state is HR cancer		**9.44**	**3.29**	**0.049**	**3,190,000**
p_TPUSB2_CNS_HR1	3.37		0.64	0.020	1,137,000
p_TPUSB2_CNS_HR2	4.56		0.61	0.020	1,539,000
p_TPUSB2_CNS_HR3	6.00		0.61	0.030	2,025,000
p_TRUSB2_CNS_HR1	3.90		0.64	0.020	1,318,000
p_TRUSB2_CNS_HR2	4.41		0.60	0.020	1,489,000
p_TRUSB2_CNS_HR3	6.18		0.65	0.030	2,087,000
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is HR cancer		**7.31**	**3.15**	**0.038**	**2,470,000**
p_TPUSB2_NC_IR1	0.04		0.24	0.000	14,350
p_TPUSB2_NC_IR2	0.43		0.33	0.000	145,100
p_TPUSB2_NC_IR3	1.19		0.46	0.010	401,000
p_TRUSB2_NC_IR1	1.37		0.51	0.010	463,700
p_TRUSB2_NC_IR2	0.08		0.24	0.000	25,350
p_TRUSB2_NC_IR3	0.70		0.41	0.000	236,000
diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is NC, and true state is IR cancer		**8.25**	**3.16**	**0.043**	**2,780,000**
p_TPUSB2_CNS_CNS1	0.80		0.47	0.000	268,700
p_TPUSB2_CNS_CNS2	0.76		0.47	0.000	255,200
p_TPUSB2_CNS_CNS3	0.80		0.43	0.000	269,700
p_TRUSB2_CNS_CNS1	1.05		0.51	0.010	355,300
p_TRUSB2_CNS_CNS2	0.92		0.48	0.000	310,500
p_TRUSB2_CNS_CNS3	0.74		0.41	0.000	248,200

diagnostic accuracy of 2nd TR & TP biopsy when 1st biopsy result is CNS, and true state is CNS cancer		**8.67**	**3.01**	**0.045**	**2,930,000**
p_TPUSB1_CNS1	0.69		0.40	0.000	233,100
p_TPUSB1_CNS2	0.75		0.43	0.000	253,500
p_TPUSB1_CNS3	0.37		0.28	0.000	123,600
p_TRUSB1_CNS1	0.59		0.37	0.000	199,300
p_TRUSB1_CNS2	0.69		0.40	0.000	232,900
p_TRUSB1_CNS3	0.56		0.31	0.000	188,200
diagnostic accuracy of 1st TR & TP biopsy when true state is CNS cancer		**5.49**	**2.77**	**0.028**	**1,850,000**
prev_CaP1	1.16		0.51	0.010	390,900
prev_CaP2	1.09		0.49	0.010	369,200
prev_CaP3	0.12		0.23	0.000	39,320
prev_CaP4	0.72		0.41	0.000	242,800
Prevalence of varying severity of CaP		**1.84**	**0.52**	**0.009**	**620,000**
p_mpMRI_CNS1	0.29		0.29	0.000	98,350
p_mpMRI_CNS2	0.11		0.27	0.000	37,030
p_mpMRI_CNS3	0.17		0.26	0.000	58,270
Diagnostic accuracy of mpMRI when true state is CNS cancer		**1.84**	**0.52**	**0.010**	**620,000**
p_mortSepsis	1.64		0.57	0.01	552,000
EVPI		£193.80	n/a	1	£65,416,000

EVPPI of individual parameters where population EVPPI > £100,000. Explanation of parameter names: Prefix p_ = probability, prev = prevalence, q = long term QALYs accrued, c= long term accrued costs. TRUSB = trans-rectal ultrasound guided biopsy. TPUSB = trans-perineal ultrasound-guided biopsy. mpMRI = multiparametric magnetic resonance imaging. Suffix 1 = outcome of NC, 2 = CNS, 3 = CS. Thus p_TPUSB2_CNS_IR3 = probability of the second TP biopsy giving a result of clinically significant cancer following a first (TP) biopsy result of CNS, when the true state of the patient is intermediate risk cancer. CC1 = no infection from biopsy; CC2 = mild infection, CC3 = urinary tract infection, CC4 = sepsis. CaP1 = prevalence of no cancer, CaP2 = prevalence of CNS cancer, CaP3 = prevalence of intermediate risk cancer, CaP4 = prevalence of high risk cancer. As = Active surveillance. Rp = radical prostatectomy.

One-way sensitivity analysis on diagnostic accuracy of TP vs TR biopsy in patients with intermediate risk cancer.

As there are three possible outcomes from the biopsy (no cancer, clinically non-significant and clinically significant), a one-way sensitivity analysis on the relative diagnostic accuracy of TP vs TR is not straightforward. For this analysis we focus only on patients whose true disease state is intermediate risk cancer, and explore the impact of changing the probability of a 'clinically significant' (CS) diagnosis with a TP biopsy as a proportion of that of the TR. In other words, the relative risk of the TP biopsy giving a CS result when the patient has IR cancer, compared with a TR biopsy. This requires adjustment of the probabilities of a no-cancer or clinically non-significant result proportionately so that the probabilities sum to 1.

For example, in patients with intermediate risk cancer, the probability of a first TR biopsy giving a result of no cancer, clinically non-significant or clinically significant result which we denote Pa, Pb and Pc is 15%, 11% and 74% respectively.

To test the impact of assuming the probability of a TP biopsy being only 90% of the sensitivity of the TR, which we define as Pc(1) the formula is:

$Pc(1) = Pc(0) * RR = 74\% * 0.9 = 66.6\%$

Pa and Pb are then adjusted according to the formulae:

$Pa(1) = (1-Pc(1)) * Pa(0)/(Pa(0) + Pb(0))$

$Pb(1) = (1-Pc(1)) * Pb(0)/(Pa(0) + Pb(0))$

An illustrative example calculated on the mean probabilities is shown in Table A6.5.

Table A6.5: Demonstration of adjusting probability of CS result for TP biopsy in patients with IR cancer

RR	p(NC)	p(CNS)	p(CS)	
Base value (TR Bx)	15.00%	11.00%	74.00%	100.00%
0.1	53.42%	39.18%	7.40%	100.00%
0.2	49.15%	36.05%	14.80%	100.00%
0.3	44.88%	32.92%	22.20%	100.00%
0.4	40.62%	29.78%	29.60%	100.00%
0.5	36.35%	26.65%	37.00%	100.00%
0.6	32.08%	23.52%	44.40%	100.00%
0.7	27.81%	20.39%	51.80%	100.00%
0.8	23.54%	17.26%	59.20%	100.00%
0.9	19.27%	14.13%	66.60%	100.00%
1	15.00%	11.00%	74.00%	100.00%

This approach was applied to the first and second biopsies simultaneously (parameters p_TPUSB1_IR, p_TPUSB2_NC_IR and p_TPUSB2_CNS_IR) to all the sampled values in the PSA. At a zero price of CamPROBE, the sensitivity must be no less than 98.8% that of the trans-rectal biopsy for it to be cost-effective (Table A6.6). At the maximum cost-effective price CamPROBE must be no less than 99.97% of the sensitivity of the trans-rectal biopsy for it to be cost-effective (Table A6.7).

Note this is not the required absolute sensitivity of CamPROBE, but the sensitivity relative to trans-rectal biopsy.

Table A6.6: One-way sensitivity analysis of relative sensitivity of TP vs TR biopsy (zero price of CamPROBE)

	TRUSBx		TPUSBx		Increments		
RR*	Cost	QALYs	Cost	QALYs	Cost	QALYs	Net Benefit**
0	5051.523	10.291	2290.034	9.905	-2761.49	-0.386	-4957.67
0.1	5051.523	10.291	2563.298	9.943	-2488.23	-0.348	-4455.84
0.2	5051.523	10.291	2836.561	9.982	-2214.96	-0.309	-3954.01
0.3	5051.523	10.291	3109.824	10.021	-1941.7	-0.27	-3452.17
0.4	5051.523	10.291	3383.088	10.06	-1668.44	-0.231	-2950.34
0.5	5051.523	10.291	3656.351	10.098	-1395.17	-0.193	-2448.5
0.6	5051.523	10.291	3929.615	10.137	-1121.91	-0.154	-1946.67
0.7	5051.523	10.291	4202.878	10.176	-848.645	-0.115	-1444.84
0.8	5051.523	10.291	4476.142	10.215	-575.381	-0.076	-943.005
0.9	5051.523	10.291	4749.405	10.254	-302.118	-0.037	-441.171
0.91	5051.523	10.291	4776.732	10.257	-274.791	-0.034	-390.988
0.92	5051.523	10.291	4804.058	10.261	-247.465	-0.03	-340.805
0.93	5051.523	10.291	4831.384	10.265	-220.139	-0.026	-290.621
0.94	5051.523	10.291	4858.711	10.269	-192.812	-0.022	-240.438
0.95	5051.523	10.291	4886.037	10.273	-165.486	-0.018	-190.255
0.96	5051.523	10.291	4913.363	10.277	-138.16	-0.014	-140.071
0.97	5051.523	10.291	4940.69	10.281	-110.833	-0.01	-89.888
0.98	5051.523	10.291	4968.016	10.285	-83.507	-0.006	-39.7047
0.981	5051.523	10.291	4970.749	10.285	-80.774	-0.006	-34.6863
0.982	5051.523	10.291	4973.481	10.285	-78.042	-0.006	-29.668
0.983	5051.523	10.291	4976.214	10.286	-75.309	-0.005	-24.6497
0.984	5051.523	10.291	4978.947	10.286	-72.576	-0.005	-19.6313
0.985	5051.523	10.291	4981.679	10.286	-69.844	-0.005	-14.613
0.986	5051.523	10.291	4984.412	10.287	-67.111	-0.004	-9.59466
0.987	5051.523	10.291	4987.144	10.287	-64.379	-0.004	-4.57633
0.9871	5051.523	10.291	4987.418	10.287	-64.105	-0.004	-4.0745
0.9872	5051.523	10.291	4987.691	10.287	-63.832	-0.004	-3.57266
0.9873	5051.523	10.291	4987.964	10.287	-63.559	-0.004	-3.07083
0.9874	5051.523	10.291	4988.238	10.287	-63.285	-0.004	-2.569
0.9875	5051.523	10.291	4988.511	10.287	-63.012	-0.004	-2.06716
0.9876	5051.523	10.291	4988.784	10.287	-62.739	-0.004	-1.56533
0.9877	5051.523	10.291	4989.057	10.287	-62.466	-0.004	-1.0635
0.9878	5051.523	10.291	4989.331	10.288	-62.192	-0.003	-0.56166
0.9879	5051.523	10.291	4989.604	10.288	-61.919	-0.003	-0.05983
0.988	5051.523	10.291	4989.877	10.288	-61.646	-0.003	0.442004
0.989	5051.523	10.291	4992.61	10.288	-58.913	-0.003	5.460338
0.99	5051.523	10.291	4995.342	10.288	-56.181	-0.003	10.47867
1	5051.523	10.291	5022.669	10.292	-28.854	0.001	60.66201

Table A6.7: One-way sensitivity analysis of relative sensitivity of TP vs TR biopsy (max price of CamPROBE, £81.17)

	TRUSBx		TPUSBx		Increments		
RR*	Cost	QALYs	Cost	QALYs	Cost	QALYs	Net Benefit**
0	5051.523	10.291	2348.913	9.905	-2702.61	-0.386	-5016.55
0.1	5051.523	10.291	2622.176	9.943	-2429.35	-0.348	-4514.72
0.2	5051.523	10.291	2895.44	9.982	-2156.08	-0.309	-4012.88
0.3	5051.523	10.291	3168.703	10.021	-1882.82	-0.27	-3511.05
0.4	5051.523	10.291	3441.967	10.06	-1609.56	-0.231	-3009.22
0.5	5051.523	10.291	3715.23	10.098	-1336.29	-0.193	-2507.38
0.6	5051.523	10.291	3988.493	10.137	-1063.03	-0.154	-2005.55
0.7	5051.523	10.291	4261.757	10.176	-789.766	-0.115	-1503.72
0.8	5051.523	10.291	4535.02	10.215	-516.503	-0.076	-1001.88
0.9	5051.523	10.291	4808.284	10.254	-243.239	-0.037	-500.05
0.91	5051.523	10.291	4835.61	10.257	-215.913	-0.034	-449.867
0.92	5051.523	10.291	4862.937	10.261	-188.586	-0.03	-399.683
0.93	5051.523	10.291	4890.263	10.265	-161.26	-0.026	-349.5
0.94	5051.523	10.291	4917.589	10.269	-133.934	-0.022	-299.317
0.95	5051.523	10.291	4944.916	10.273	-106.607	-0.018	-249.133
0.96	5051.523	10.291	4972.242	10.277	-79.281	-0.014	-198.95
0.97	5051.523	10.291	4999.568	10.281	-51.955	-0.01	-148.767
0.98	5051.523	10.291	5026.895	10.285	-24.628	-0.006	-98.5833
0.99	5051.523	10.291	5054.221	10.288	2.698	-0.003	-48.4
0.991	5051.523	10.291	5056.954	10.289	5.431	-0.002	-43.3816
0.992	5051.523	10.291	5059.686	10.289	8.163	-0.002	-38.3633
0.993	5051.523	10.291	5062.419	10.29	10.896	-0.001	-33.345
0.994	5051.523	10.291	5065.152	10.29	13.629	-0.001	-28.3266
0.995	5051.523	10.291	5067.884	10.29	16.361	-0.001	-23.3083
0.996	5051.523	10.291	5070.617	10.291	19.094	0	-18.29
0.997	5051.523	10.291	5073.349	10.291	21.826	0	-13.2716
0.998	5051.523	10.291	5076.082	10.291	24.559	0	-8.25329
0.999	5051.523	10.291	5078.815	10.292	27.292	0.001	-3.23496
0.9991	5051.523	10.291	5079.088	10.292	27.565	0.001	-2.73313
0.9992	5051.523	10.291	5079.361	10.292	27.838	0.001	-2.23129
0.9993	5051.523	10.291	5079.635	10.292	28.112	0.001	-1.72946
0.9994	5051.523	10.291	5079.908	10.292	28.385	0.001	-1.22763
0.9995	5051.523	10.291	5080.181	10.292	28.658	0.001	-0.72579
0.9996	5051.523	10.291	5080.454	10.292	28.931	0.001	-0.22396
0.9997	5051.523	10.291	5080.728	10.292	29.205	0.001	0.277873
0.9998	5051.523	10.291	5081.001	10.292	29.478	0.001	0.779707
0.9999	5051.523	10.291	5081.274	10.292	29.751	0.001	1.28154
1	5051.523	10.291	5081.547	10.292	30.024	0.001	1.783374